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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/779,746	02/18/2004	Sheldon B. Greer	2954-128	2050

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EXAMINER
ANDERSON, JAMES D

ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
08/13/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/779,746	GREER, SHELDON B.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-24,28-33 and 39-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-24,28-33 and 39-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

CLAIMS 22-24, 28-33 & 39-59 ARE PRESENTED FOR EXAMINATION

Applicants' amendment filed 5/21/2007 has been received and entered into the application. Accordingly, claims 22, 24, 29-32 and 39-42 have been amended.

The above amendments and Applicants' remarks have overcome the rejections not reiterated herein from the previous office action. Such rejections are hereby *withdrawn*. However, upon further consideration the following rejections are newly applied and constitute the totality of issues remaining in the present application.

Claim Rejections - 35 USC § 112 (2nd Paragraph)

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 49, 52, 55 and 57-58 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear what is meant by the phrases "tumor implicates hypermethylation" and "tumor implicates gene silencing". For example, is it Applicant's intent that the tumor being treated *results from* hypermethylation or gene silencing?

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 22-24, 28-29, 32, 39, 42-44 and 47 are rejected under 35 U.S.C. § 102(b) as being anticipated by Greer (WO 85/01871; Published May 9, 1985) (prior art of record).

The Greer reference was applied in the Office Action mailed 8/24/2006 in 35 U.S.C. § 103 rejections of the present claims. Said rejection was withdrawn in view of Applicant's declaration filed 2/26/2007, which cited the unpredictability of the art and unexpected results. However, upon further consideration of the claimed subject matter, it is apparent to the Examiner that the Greer reference anticipates the claimed methods for the following reasons.

Instant claim 22 recites a method a treating a human tumor comprising two steps. First, said tumor is sensitized to radiation by administering to a patient 5-chloro-2'-deoxycytidine and tetrahydrouridine. Second, the patient is exposed to an effective level of radiation to treat said tumor. The Examiner notes that radiation therapy is commonly used to treat tumors. As such, exposing a patient having a tumor to radiation will normally result in treatment of the tumor to some degree, whether or not 5-chloro-2'-deoxycytidine and tetrahydrouridine are administered prior to such radiation.

Greer teaches a method of sensitizing neoplastic tissue to radiation comprising the administration of 5-chlorodeoxycytidine (5-CldC) co-administered with tetrahydrouridine (H_4U) (Abstract). The reference thus explicitly teaches step one of the instant claims. The invention of Greer provides therapeutic materials and procedures for treating solid tumors using X-ray or gamma ray, beta, neutron and other radiation sources (page 2, lines 10-15). According to one aspect of the invention, patients having tumors requiring radiation therapy are administered, preferably on a slow release basis, 5-chloro-2'-deoxycytidine and/or 5-chloro 2'-halo-2'-deoxycytidine. The deoxycytidine compound is preferably administered with a deamination

inhibitor, preferably tetrahydrouridine, for a period of time until amounts sufficient to sensitize tumor tissue to radiation are present in the tumor tissue (page 3, lines 4-14). The reference thus explicitly teaches administering a combination of 5-chloro-2'-deoxycytidine and tetrahydrouridine to a patient having a tumor about to undergo radiation therapy. The slow release formulations of Greer anticipate the limitations of instant claim 24. Low concentrations of tetrahydrouridine are taught to protect the nucleoside analogs from systematic catabolism whereas with high concentrations of tetrahydrouridine, CldC "should be converted preferentially at the tumor site to CldUMP in human tumors possessing high levels of deoxycytidine kinase and dCMP deaminase (page 9, lines 20-28). Claims 1-4 of the WO document explicitly recite methods of sensitizing "susceptible neoplastic tissue" to radiation by administering the instantly claimed compounds. Although pretreatment with an inhibitor of pyrimidine biosynthesis (*e.g.*, the agents excluded from the methods instantly claimed) is also disclosed in the reference, it is clear that Greer also unequivocally teaches administering a combination of 5-chloro-2'-deoxycytidine and tetrahydrouridine so as to sensitize tumors to radiation therapy (page 3, lines 4-14). While such therapy may be *enhanced* by co-administration with an inhibitor of pyrimidine biosynthesis, the fact remains that 5-chloro-2'-deoxycytidine and tetrahydrouridine are alone effective to sensitize tumors to radiation when administered without such an inhibitor of pyrimidine biosynthesis.

Applicant has argued (see Response filed 2/26/2007) that the Greer reference "strongly teaches (and requires) the use of PALA and FdC (or FdU)" as a pretreatment step in the method of treating neoplastic tissue in a patient by administering 5-chloro-2'-deoxycytidine and tetrahydrouridine to and irradiating the patient (page 8 of Response) (emphasis added).

However, as noted *supra*, a method of treating a tumor with radiation does not *require* any type of chemical treatment prior to such irradiation. Irradiation is generally effective to kill both cancerous and non-cancerous cells. Further, page 3, lines 4-14 of the reference clearly teaches that patients having tumors requiring radiation therapy are administered, preferably on a slow release basis, 5-chloro-2'-deoxycytidine, which is preferably administered with a deamination inhibitor, preferably tetrahydrouridine. While "optimally" the patient is given a pretreatment regimen, such pretreatment is not required in the methods of Greer.

The instantly claimed methods only require that a tumor be treated when a patient is administered 5-chloro-2'-deoxycytidine and tetrahydrouridine followed by an effective level of radiation. It is clear from the Greer reference that administration of 5-chloro-2'-deoxycytidine and tetrahydrouridine is effective to sensitize tumors to irradiation. As such, Greer clearly anticipates the claimed method of treating tumors comprising sensitizing tumors to radiation by administering 5-chloro-2'-deoxycytidine and tetrahydrouridine and exposing a patient to an effective level of radiation.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 30-31 and 40-41 are rejected under 35 U.S.C. § 103(a) as being obvious over Greer (WO 85/01871; Published May 9, 1985) in view of Shepherd *et al.* (Cancer, 1992, vol. 70, pages 2250-2254, Abstract) (prior art of record).

Greer teach as applied to claims 22-24, 28-29, 32, 39, 42-44 and 47, *supra*. Greer does not explicitly teach the use of yttrium-90 as a radiation source.

However, Shepherd *et al.* disclose that yttrium-90 microspheres have been used in the treatment of primary hepatocellular carcinoma (Abstract).

Thus, the instantly claimed methods wherein the radiation source comprises yttrium 90 needles would have been *prima facie* obvious in view of Shepherd *et al.* who teach that yttrium-90 is a radiation source used in the treatment of cancer. The skilled artisan would be imbued with at least a reasonable expectation that yttrium-90 would be a viable source of radiation in the treatment methods of Greer. The motivation to use other radiation sources is clearly found in Greer, who teaches that radiation can be from "other radiation sources", aside from those explicitly disclosed (page 2, lines 10-15).

Claims 33, 45-46, 48, 50-51, 53-56 and 58-59 are rejected under 35 U.S.C. § 103(a) as being obvious over Greer (WO 85/01871; Published May 9, 1985).

Greer teach as applied to claims 22-24, 28-29, 32, 39, 42-44 and 47, *supra*. Greer does not explicitly teach the treatment of the specific tumors (*e.g.*, lung, prostate, breast, etc.) recited in the instant claims. The reference also does not explicitly teach the treatment of tumors resulting from gene silencing.

However, given the broad teachings of Greer as discussed *supra*, the skilled artisan would reasonably expect that the methods of sensitizing tumors to irradiation as taught in Greer could be predictably used to treat tumors of different organs. It is recognized in the art that radiation therapy is a useful, predictable treatment of tumors of different origin and etiology. As

such, the skilled artisan could readily apply the methods of Greer to patients having tumors in different organs or arising from a different natural or environmental cause.

Claims 49, 52 and 57 are rejected under 35 U.S.C. § 103(a) as being obvious over Greer (WO 85/01871; Published May 9, 1985) in view of Nagatake *et al.* (Cancer Research, 1996, vol. 56, pages 1886-1891) (prior art of record).

Greer teach as applied to claims 22-24, 28-29, 32, 39, 42-44 and 47, *supra.* Greer does not teach the treatment of a tumor implicated by hypermethylation.

However, Nagatake *et al.* disclose that hypermethylation of DNA is recognized as a consistent molecular change in human cancers, including lung cancer (page 1886, left column, first paragraph).

Thus, the instantly claimed methods of treating tumors caused by hypermethylation of nucleic acids would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Greer discloses a method of sensitizing neoplastic tissue to radiation comprising the administration of 5-chlorodeoxycytidine (5-CldC) co-administered with tetrahydrouridine (H_4U) (Abstract). Nakatake *et al.* disclose that altered DNA methylation may play a role in the oncogenesis of human neoplasms, including lung cancer. The skilled artisan would be imbued with at least a reasonable expectation that the methods disclosed in Greer could be used to treat tumors caused by hypermethylation of nucleic acids because the Greer reference is clearly not limited to the treatment of any particular tumor of specific etiology. Further, the skilled artisan could predictably use irradiation to treat any tumor of any etiology. Such methods of treating tumors with irradiation are commonplace in the art of treating cancer.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson
Patent Examiner
AU 1614

August 2, 2007

Ardin H. Marschel 8/5/07
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SUPERVISORY PATENT EXAMINER